



Short communication

Aerobic oxidation of amines to imines catalyzed by a ruthenium complex under solvent-free conditions



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ABSTRACT

A ruthenium complex $[\text{Et}_3\text{NH}]_2[\text{Ru}(\text{dipic})\text{Cl}_3]$ showed high efficiency in the homo-coupling of primary amines and cross-coupling of benzylamine with anilines and aliphatic amines to the corresponding imines under air and solvent-free conditions. This protocol is an atom-economical green process and tolerates various substrates bearing both electron-donating and electron-withdrawing substituents.

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1. Introduction

Imines are key synthetic intermediates in many reactions such as reductions, condensations, additions, cycloadditions, and also important class of compounds used in the synthesis of numerous biologically and pharmaceutically active compounds [1–4]. Traditionally, imines are synthesized by the condensation reaction of carbonyl compounds with primary amines in the presence of an acid catalyst. Due to the need for organic and pharmaceutical syntheses, exploring new methods for the synthesis of various imines is still an essential task faced by chemists.

In recent years, a number of methods for the synthesis of imines have been developed such as oxidative cross-coupling between amines and alcohols [5–7], oxidation of secondary amines [8,9], and self-condensation of primary amines with oxidant [10,11]. The self-condensation of primary amines to imines has the advantage of ready availability of amines. Therefore, a wide variety of catalysts such as metal (especially non-noble biocompatible metals copper, cobalt and iron) [12–17], metal-free [18–21], photo- [22–26], and bioinspired [27–30] catalysts have been developed and bring big developments to this approach. Among the catalytic systems the transition metal based catalytic systems, which tolerate important substrate classes, afford imines in good yields and with high selectivity. However, some of the metal-based catalytic systems still have some disadvantages such as

requiring pure oxygen, high oxygen pressure, solvent and (or) other auxiliaries to obtain high yields. Therefore, it is essential to develop simple catalytic systems with high efficiency for the aerobic oxidation of primary amines to imines under mild conditions. We focus on ruthenium complexes as catalysts to get this goal because some ruthenium based catalysts proved to be very active in the cross-coupling between amines and alcohols [31,32], oxidation of secondary amines to imines [33], and homo-coupling of amines to imines via hydrogen transfer without oxidant [34]. We found that a mononuclear ruthenium complex $[\text{Et}_3\text{NH}]_2[\text{Ru}(\text{dipic})\text{Cl}_3]$ (dipic = 2,6-pyridinedicarboxylate, dipicolinate) which is easily synthesized from RuCl_3 , triethylamine and dipicH_2 showed excellent performance in the self-condensation of primary amines to imines with air as oxidant under solvent-free and atmospheric pressures.

2. Experimental

2.1. Materials and apparatus

The primary amines and 2, 6-pyridinedicarboxylic acid (dipicH_2) were obtained from Alfa Aesar China (Tianjin) Co., Ltd. All reagents were used as received without further purification. The ruthenium complex $[\text{Et}_3\text{NH}]_2[\text{Ru}(\text{dipic})\text{Cl}_3]$ was prepared as described in the literature [35].

^1H MNR spectra of imines were recorded with TMS as internal standard on a Bruker AC-P 400 spectrometer. Oxidation reaction samples were analyzed on a Shandong Lunan Ruihong Gas Chromatograph (SP-6800A) equipped with a FID detector and a SE 30 column (30 m \times 0.5 μm).

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2.2. Catalytic oxidation

In a typical process, into a 5 ml two-necked, round-bottom flask equipped with a magnetic stirrer was added $[\text{Et}_3\text{NH}]_2[\text{Ru}(\text{dipic})\text{Cl}_3]$ (0.005 mmol 0.01 equiv.) and benzylamine (5 mmol 1 equiv.) at room temperature successively. After which the resulting reaction mixture was heated at 100 °C for 10 h in an air atmosphere. The final reaction conversion and selectivity towards the corresponding imines were determined by ^1H NMR. After completion of the reaction, the product was received by column chromatography of the reaction mixture on neutral alumina using hexanes/EtOAc (95:5) as eluent.

3. Results and discussion

The complex $[\text{Et}_3\text{NH}]_2[\text{Ru}(\text{dipic})\text{Cl}_3]$ being active in self-condensation of primary amines to imines was found occasionally in our study of aerobic oxidation of benzylamine to benzonitrile using this complex as catalyst in acetonitrile. The major product identified was *N*-(benzylidene)benzylamine. Therefore, we turned our attention to the self-condensation of benzylamine to *N*-(benzylidene)benzylamine. First, the reaction was run in solvent and solvent-free conditions under air, respectively. Reaction was not efficient in acetonitrile (Table 1, entry 1), only moderate yield of target product was obtained. The reaction was more efficient in trifluorotoluene (Table 1, entry 2) but still with about 10% of benzonitrile as byproduct. To our delight, the reaction proceeded smoothly under solvent-free conditions, *N*-(benzylidene)benzylamine was obtained almost quantitatively (Table 1, entry 4). This is attractive from the point of view of green chemistry.

The effect of reaction parameters on the reaction was investigated under solvent-free conditions, and the results are shown in Table 1. As can be seen from Table 1, increasing the complex loading from 0.5 mol% to 1.5 mol% led to fast reaction, the reaction time required to finish the reaction decreased from 18 h to 8 h. Meanwhile, the yield increased from 97% to higher than 99% (Table 1, entries 3–5). Increasing reaction temperature can accelerate the reaction, and increase the yield of *N*-(benzylidene)benzylamine (Table 1, entries 4, 6, 7). It is unexpected that pure oxygen (balloon on the top) as oxidant gave low yield compared to air (Table 1, entries 4, 6, 7), which could be ascribed to impossible discharge of ammonia generated in the self-condensation of benzylamine due to the plugging of the balloon.

Control experiments were performed to evaluate the necessity of the complex in the reaction. As shown in Table 1, the use of complex

$[\text{Et}_3\text{NH}]_2[\text{Ru}(\text{dipic})\text{Cl}_3]$ is essential. No reaction was observed when no $[\text{Et}_3\text{NH}]_2[\text{Ru}(\text{dipic})\text{Cl}_3]$ was charged. RuCl_3 instead of $[\text{Et}_3\text{NH}]_2[\text{Ru}(\text{dipic})\text{Cl}_3]$ as catalyst led to the yield of *N*-(benzylidene)benzylamine as low as 30% in 15 h (Table 1, entry 11). Under the nitrogen atmosphere, very low yield (13%) of *N*-(benzylidene)benzylamine was obtained, which indicated that the formation of *N*-(benzylidene)benzylamine was through an oxidative dehydrogenation but not through a direct dehydrogenation of benzylamine. From the results we found the optimal amount of the ruthenium complex to be 1 mol% of benzylamine, and the suitable reaction temperature to be 100 °C.

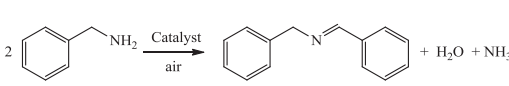
For evaluating the versatility of this novel catalytic system, the oxidative homo-coupling of various amines to the corresponding imines was explored under the optimized reaction conditions, and the results are shown in Table 2. As shown in Table, most of benzyl amines, including those bearing both electron-withdrawing and electron-donating groups *para* or *meta* to aminomethyl group, were converted to the corresponding imines in good to excellent yields under the optimized reaction conditions (Table 2, entries 1–8, 10). But the time required to finish the reaction was different. Generally, the electron-withdrawing substituents led to a longer reaction time (Table 2, entries 2, 6, 8). These results demonstrated that electronic properties of the substituents seem to have some effects on the reaction. It is obvious that the position of the substituent on the benzene ring has certain effects on the reactivity of benzyl amines, too. The substrate with an *o*-substituent showed poor reactivity compared to that with an *m*- or *p*-substituent due to the steric hindrance (Table 2, entries 9, 11). For instance, only 50% yield of the corresponding imine was obtained in 18 h in the case of *o*-fluorobenzyl amine as a substrate (Table 2, entry 11). Aldehydes as by-products were observed in the cases that the selectivity of imines was lower than 100%. The aldehyde by-products were derived from the hydrolysis of imine intermediates in the reaction.

The complex also showed high activity in the oxidative coupling of heterocyclic amines such as 2-thioly methylamine. 2-Thioly methylamine was converted to the corresponding imine in a yield as high as 95% in 15 h. Generally, heterocyclic amines were poor substrates in the oxidative homo-coupling of amines to imines catalyzed by copper-based [13]. Moderate yields of the corresponding imines were received in the homo-coupling of non-activated aliphatic amines at 1% of catalyst loading (Table 2, entries 14–17). When the catalyst loading was increased to 1.5%, the yields of the corresponding imines were improved largely (Table 2, entries 14–21). For instance, in the case of cyclohexylmethylamine as a substrate, the yield of the corresponding imine reached 81% (GC yield) (Table 2, entry 21).

In subsequent studies, the complex was evaluated in the synthesis of unsymmetrically substituted imines, which were carried out by reacting benzylamines with various substituted anilines under conditions obtained above. Anilines bearing both electron-donating and weak electron-withdrawing substituents afforded good yields of cross-coupled imines (Table 3, entries 1–5). Thus, except in the case of the *p*-nitro group, the presence of substituents in *para* or *meta* position with respect to the amino group increased the selectivity in favor of the unsymmetrical imine **A** (Table 3, entries 2–7). Increasing the molar ratio of 4-methyl phenylamine to benzylamine increased the selectivity of the cross-coupling product (Table 3, entries 2, 3). The reaction of benzylamine with *p*-nitroaniline bearing a strong electron-withdrawing nitro group, however, produced only the symmetrical imine **B** (Table 3, entry 6), which can be ascribed to the low nucleophilicity of *p*-nitroaniline compared to benzylamine. This was also observed in the copper catalyzed cross-coupling of amines [10].

The catalyst was also evaluated in the synthesis of scarcely stable aliphatic imines. Symmetrical imine **B** (10%) was observed at the molar ratio of hexylamine to benzylamine of 2:1 (Table 3, entry 10). Increasing the molar ratio of hexylamine to benzylamine remarkably improved the selectivity to the unsymmetrical imine **A**. Complete selectivity to **A** at quantitative conversion of benzylamine was achieved at the molar ratio of hexylamine to benzylamine of 3:1 (Table 3, entry

Table 1
Optimization of the conditions for the oxidative coupling of benzylamine to imines.



Entry	Catalyst (mol%)	Solvent	Temperature (°C)	Time (h)	Yield ^a (%)
1	1.0	MeCN	Reflux	24	77
2	1.0	PhCF ₃	Reflux	10	90
3	0.5	–	100	18	97
4	1.0	–	100	10	>99
5	1.5	–	100	8	>99
6	1.0	–	80	20	84
7	1.0	–	120	8	>99
8	0	–	100	10	0
9 ^b	1.0	–	100	6	79
10 ^c	1.0	–	100	10	13
11 ^d	1.0	–	100	15	30

Reaction conditions: benzylamine (5 mmol), running reaction under open air atmosphere.

^a Yield was determined by GC based on area%, the selectivity of imine was 100%.

^b Reaction was performed under an oxygen balloon.

^c Reaction was performed under a nitrogen atmosphere.

^d RuCl_3 instead of $[\text{Et}_3\text{NH}]_2[\text{Ru}(\text{dipic})\text{Cl}_3]$ was used as catalyst.

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